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10/717,597	11/21/2003	Natalie C. Twine	AM101055	3640

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,597	TWINE ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/30/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8 and 21-30* is/are pending in the application.

4a) Of the above claim(s) *22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-8 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/11/08 has been entered.

Claim Status

2. Claims 2 and 9-20 have been canceled as filed on 6/8/07.

Claims 21-30 have been added as filed on 6/8/07.

Claims 1, 3-8 and 21-30 are currently pending.

Claims 22-30 have been withdrawn due to non-elected inventions.

Claims 1, 3-8 and 21 are being examined in this application.

Election/Restrictions

3. Applicant's election with traverse the "combination of EEF1A (SEQ ID NO:285) and TLR2(SEQ ID NO: 1 and 240)" in the reply filed on 7/30/08 is acknowledged. The traversal is on the ground(s) that the inventions are related because "the genes are capable of use together"; "the different genes will produce the same result"; and "the different genes have the same function". This is not found persuasive because each group of invention would use different combination of genes that possesses distinct function and/or structures. The different genes

would not share the same core structure, and would also have different properties (such as encoding for different proteins) and therefore different functions. For example, the different nucleic acid sequences can encode for different proteins, which the different proteins would not share the same core structure, and would also have different properties (such as 3-D folding structures and target binding properties) and therefore different functions. Thus, these different nucleic acids would have different modes of operation, different effects, and can be used in different methods. For example, an alignment between (SEQ ID NO 285; the EEF1A2 gene) and (SEQ ID NOs:1 and 240; representing TLR2 gene) do not result in substantial overlapping sequences and thus the sequences are mutually exclusive and distinct. In addition, a search of multiple sequences would impose undue search burden on the office. See MPEP 803.04 (especially for guidance on claiming combinations of nucleic acids) and Pre-OG Notice (published 3/27/07; signed 2/22/07) rescinding the "partial waiver" for nucleic acid sequences. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Art anticipating or rendering obvious each of the above identified groups respectively would not necessarily anticipate or render obvious another group, because they are drawn to different inventions that have different distinguishing features and/or characteristics. Consequently, the different invention groups have different issues regarding patentability and enablement and represent patentably distinct subject matter. Thus, the different invention groups are distinct, and restriction between the groups is proper.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 22-30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/30/08. The instant claims 22-30 have been amended to recite various combination of genes or method of using the said various combinations of genes, which the different combinations of genes are distinct as discussed supra, and thus do not read on the elected invention of the specific combination of two genes, EEF1A2 and TLR2 genes.

5. Applicant's election with traverse of the following species:

A.) TLR2 as the first specific gene and EEF1A2 as the second specific gene;

in the reply filed on 7/30/08 is acknowledged.

Priority

6. This application claims priority to provisional applications 60/427,982 filed on 11/21/2002, and 60/459,782 filed on 04/03/2003.

Specification

7. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. MPEP 608.01.

Claim Rejections Withdrawn

8. In light of applicants' amendments to the claims and upon further consideration, the following claim rejections as set forth in the previous office action are withdrawn:

A.) Claims 8-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over McKiernan et al (US 6,087,098; 7/11/2000; cited in IDS), in view of Young et al (American Journal of Pathology. Vol. 158(5): 1639-1651; 5/2001), Golub et al (Science. Vol. 286: 531-527; 1999; cited previously) and Liu et al (Infection and Immunity. Vol. 69: 2788-2796; 2001; cited previously).

B.) Claims 1, 3-8 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the gene expression profile of the combination of the 20 genes listed in Table 10 (Example 8) to indicate RCC at the tumor stage when compared to the gene expression profiles of disease free individuals, does not reasonably provide enablement for using any other genes or combination of genes and their expression profiles for the purpose of indicating the presence and absence of RCC in any human (such as the ones with other diseases.

C.) Claims 1, 3-8 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description Rejection

10. Claims 1, 3-8 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite a method for diagnosis of renal cell carcinoma (RCC), the method comprising the steps of: (a) providing at least one peripheral blood sample of a human; (b) generating an expression profile comprising expression levels of one or more RCC disease genes in said at least one peripheral blood sample of the human; (c) comparing the expression profile generated in step (b) to at least one reference expression profile comprising expression levels of said two or more RCC disease genes wherein the reference expression profile is obtained from peripheral blood samples from patients having RCC and/or peripheral blood samples for disease-free humans, where in differential expression of said two or more RCC genes in said comparison is indicative of the presence or absence of RCC in the human; and wherein said two or more RCC disease genes are selected from the group consisting of: eukaryotic elongation factor 1 alpha 2 (EEF1A2); toll-like receptor 2 (TLR2)...

To satisfy the written description requirement, applicants may convey reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. See, e.g., Vas-Cath, 935 F.2d at 1565, 19 USPQ2d at 1118.

The written description requirement of 35 U.SC. 112 exists independently of enablement requirement, and the requirement applies whether or not the case involves questions of priority. The requirement applies to all inventions, including chemical inventions, and because the fact that the patent is directed to method entailing use of compound, rather than to compound per se, does not remove patentee's obligation to provide a description of the compound sufficient to distinguish infringing methods from non-infringing methods. See Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 920-23, 69 USPQ 2d 1886, 1890-93 (Fed. Cir. 2004).

With regard to the description requirement, applicants' attention is invited to consider the decision of the Court of Appeals for the Federal Circuit, which holds that a "written description of an invention involving a chemical genus, like a description of a chemical species,

'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it form other materials." University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1405 (1997), quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original) [The claims at issue in University of California v. Eli Lilly defined the invention by function of the claimed DNA (encoding insulin)].

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical an/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

The instant claims are drawn to a method using a genus of genes for diagnosing (i.e. indicating "the presence or absence of RCC in the human") RCC. The broad independent Claim 1 is drawn to a genus of genes and/or any combination thereof, and a genus of "expression profiles" (including individual genes or any combination thereof). Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of genes and the genus of gene expression profiles that can be used to diagnose RCC specifically. In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genus of genes and genus of expression profiles.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. (see MPEP 2163 II).

In this case, the instant application does not specifically disclose which individual genes or combination thereof would provide gene expression profiles that can be used to diagnose RCC

specifically. In addition, some of the genes listed in the specifications (such as the ones listed in Tables 4 and 6) are also known to be indicative of other cancers (e.g. [0150], [0214], [0269], etc.). For example, the so called TLR2 gene is known in the art to be over-expressed in individual with immunoactivation such as bacterial infection (see **Liu** et al., Infection and Immunity. Vol. 69(5): 2788-2796; 2001; cited previously). In fact, the toll-like receptor 2 (or TLR2) is not specifically linked to any particular disease, but is involved in the immune activation system in general (see **Palsson-McDermott** et al., Ir J. Med. Sci. Vol.176: 253-260; 2007). The article by Palsson-McDermott reviews the physiological role of TLR2 as well as its implications in various diseases (e.g. Abstract). The McDermott reference teaches "TLR2 has been implicated in several auto-immune and inflammatory conditions" (e.g. Abstract; Table 1; p.255). In addition, El-Omar (**El-Omar** et al., Oncogene. Vol.27: 244-252; 2008) also teaches TLRs in general are associated with numerous diseases including cancer (e.g. Abstract; p.246). Thus, the TLR2 gene is not shown to be associated with a particular disease, but the said gene is linked with various different diseases. In other words, a differential expression of the TLR2 gene does not conclusively indicate an occurrence of "RCC" specifically.

Further, **Anand** et al (Nature Genetics. Voll. 31: 301-305; 2002; cited previously) teach the overexpression of the EEF1A2 gene is observed in ovarian cancer tumors (see Abstract of Anand). Thornton et al (**Thornton et al.**, J. Mol. Med. Vol.81: 536-548; 2003) reviews the role of elongation factor 1α2 (EEF1A2) (see entire document). The Thornton reference teaches the "elongation factors have important regulatory roles in cell growth, apoptosis, and tumorigenesis" (e.g. Abstract). The reference also teaches EEF1A2 is a part of a collection of housekeeping genes (e.g. pp.537+), i.e. a general required gene for normal cellular functions (e.g. protein

synthesis). The reference also teaches EEF1A2 is an oncogene (i.e. promoting cancer). Thus, the EEF1A2 gene is also not shown to be particularly linked to RCC, but it has general implication in various diseases (including various cancers).

It is not known in the art that all genes listed in the instant claim 1 are "differentially expressed" in RCC patient as compared to other diseased or disease-free individual. For examples, if a patient having ovarian cancer would have differentially expressed EEF1A2 gene as well as TLR2 gene (due to its role in the immune pathway) when compared to a disease-free person or to a person having RCC. Thus, a clear diagnosis of RCC for the said patient would not be possible by relying on the expression profiles of the TLR2 and the EEF1A2 genes. That is at least for the methods of specifically diagnosing RCC using the expression profiles of individual genes or combinations thereof are highly unpredictable.

The instant specification only provides examples (e.g. Example 6) where the expression profiles of genes from RCC patient are compared to diseases free individuals, but not to patients with other diseases. In addition, the instant specification only provides examples of correlating gene expression profiles from RCC patients with tumors (i.e. later stage of RCC) to disease free individuals. The instant specification does not provide support for the entire claimed genus of methods of "diagnosing" RCC at any stage of the disease. That is applicants have not shown the correlation observed between gene expression profiles of RCC tumor and disease free tissues are predictive to "diagnosis" of RCC at any stage of the disease or to differentiating RCC from other diseases.

Thus, applicants do not appear to have possession of the entire claimed genus of methods of using any one or more of the listed "RCC disease genes" for specifically diagnosing RCC.

One of ordinary skilled in the art would not be able to specifically diagnose RCC based on any individual gene expression and/or combination thereof of the listed genes. Without generating the desired gene expression profile, the claimed method of diagnosis cannot be accomplished.

Applicants also do not possess the entire genus of gene expression profiles for diagnosing or indicating the "presence or absence of RCC in the human". As stated in the instant specification, the genes listed in Tables 4 and 6 may also be differentially expressed in patients with other diseases than RCC. (e.g. [0045]). The instant specification also states "it is suggestive that the human subject may be infected with RCC (or other solid tumors, depending on the genes used in the diagnosis)" ([0492]), which indicates that further experimentation is needed to distinguish RCC from other diseases using gene expression profiles. Thus, it is highly unpredictable to use various genes and their expression profiles for diagnosing RCC. The instant specification does not provide all possible combination (or subcombinations) of genes or individual genes (from the claimed list) that can be used to differentiate RCC from other tumor diseases. The instant specification only recites examples of using samples derived from patients known to have RCC or persons that were known to be disease-free (see Example 1 of the instant spec.). It is also not clear what specific differential expression profiles (such as over- or under-expression) of the various sets of genes are correlated with a positive RCC diagnosis. For example, an over expression of two genes (such as TLR-2 and EEF1A2) may not create an expression profile to distinguish among different diseases. As discussed supra, overexpression of the said genes (TLR2 and EEF1A2) may be indicative of bacteria infection and/or ovarian cancer. In addition, data in Table 6 (and [0589] of the spec.) indicates that at least 16 genes are presented only in one sample (a single patient), and more genes are only presented in few than 6

patients (~10% of total sample size), which would not be representative or statistically significant to show possession of the claimed method. This also indicates high unpredictability of using these genes for diagnosing RCC in any human.

Thus, applicant's claimed scope represents only an invitation to experiment regarding possible genes and gene expression profiles that might be used for the purpose of indicating the presence and absence of RCC in human.

Therefore, applicants are not in possession of a claimed genus of "RCC disease genes" and the various gene expression profiles as well as the genus of methods that are using the various gene expression profiles to diagnose RCC. Applicant's claimed scope represents only an invitation to experiment regarding possible genes and gene expression profiles that might be used for the purpose of indicating the presence and absence of RCC in human.

Discussion and Answer to Argument

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the claim amendment is sufficient to overcome the previously set forth written description rejection. (Reply, pp.9+).

However, applicant's amendments to the claims are not sufficient to overcome the written description rejection as set forth previously as well as the reasons discussed above.

Applicants also assert "the specification specifically discloses combinations of genes that can be used to diagnose RCC in a patient". (Reply, pp.10+).

Applicants specifically pointed to "Example 6" of the instant specification for support. Example 6 of the instant disclosure describes using samples isolated from either patients known to have RCC or "normal PBMC samples" (i.e. disease-free samples) (e.g. [0605]). In the said Example, the "prediction" of RCC is done on the samples of the "test set", which the test set comprise samples from either samples known with RCC or samples that are disease-free (e.g. [[0601]). That is the "comparison" is between a known RCC sample and a normal tissue sample. In this Example, the gene expression profiles of the RCC samples were not compared to other diseased samples (such as other tumor samples), to show a RCC specific differential expression pattern. Further, the said Example 6 also does not show "predicting" or diagnosing RCC using truly "unknown" samples (without prior diagnosis) based on the claimed set (or subset) of genes. That is the instant specification does not have support for a method of "diagnosing" or "predicting" RCC in any individual based on comparison of the expression profiles of any set or subset of genes claimed.

New Claim Objection(s) / Rejection(s)

Claim Rejections - 35 USC § 112

Enablement Rejection

12. Claims 1, 3-8 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. §112, first paragraph, have been described *In re Wands*, 8 USPQ2d 1400(1988). They are:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The predictability or lack thereof in the art
5. The level of skill in the art;
6. The amount of direction or guidance present;
7. The presence or absence of working examples;
8. The quantity of experimentation needed.

The breadth of the claims / The nature of the invention

The instant claims are drawn to a method using at a genus of genes and/or combination thereof for diagnosing (i.e. indicating "the presence or absence of RCC in the human") RCC. The broad independent Claim 1 is drawn to a genus of genes and/or any combination thereof, and a genus of "expression profiles" (including individual genes and/or any combination thereof).

The state of the prior art/ The predictability or lack thereof in the art

The instant application does not specifically disclose which individual genes or combination thereof would provide gene expression profiles that can be used to diagnose RCC

specifically. In addition, some of the genes listed in the specifications (such as the ones listed in Tables 4 and 6) are also known in the art to be indicative of other cancers (e.g. [0150], [0214], [0269], etc. of the instant specification). For example, the so called TLR2 gene is known in the art to be over-expressed in individual with immunoactivation such as bacterial infection (see Liu et al., Infection and Immunity. Vol. 69(5): 2788-2796; 2001; cited previously). In fact, the toll-like receptor 2 (or TLR2) is not specifically linked to any particular disease, but is involved in the immune activation system in general (see Palsson-McDermott et al., Ir J. Med. Sci. Vol.176: 253-260; 2007). The article by Palsson-McDermott reviews the physiological role of TLR2 as well as its implications in various diseases (e.g. Abstract). The McDermott reference teaches "TLR2 has been implicated in several auto-immune and inflammatory conditions" (e.g. Abstract; Table 1; p.255). In addition, El-Omar (El-Omar et al., Oncogene. Vol.27: 244-252; 2008) also teaches TLRs in general are associated with numerous diseases including cancer (e.g. Abstract; p.246). Thus, the TLR2 gene is not shown to be associated with a particular disease, but the said gene is linked with various different diseases. In other words, a differential expression of the TLR2 gene does not conclusively indicate an occurrence of "RCC" specifically.

Further, Anand et al (Nature Genetics. Voll. 31: 301-305; 2002) teach the overexpression of the EEF1A2 gene is observed in ovarian cancer tumors (see Abstract of Anand). Thornton et al (Thornton et al., J. Mol. Med. Vol.81: 536-548; 2003) reviews the role of elongation factor 1α2 (EEF1A2) (see entire document). The Thornton reference teaches the "elongation factors have important regulatory roles in cell growth, apoptosis, and tumorigenesis" (e.g. Abstract). The reference also teaches EEF1A2 is a part of a collection of housekeeping genes (e.g. pp.537+), i.e. a general required gene for normal cellular functions (e.g. protein synthesis). The reference also

teaches EEF1A2 is an oncogene (i.e. promoting cancer). Thus, the EEF1A2 gene is also not shown to be particularly linked to RCC, but it has general implication in various diseases (including various cancers).

To further indicate the unpredictability of the instant claimed method, the instant specification also states "it is suggestive that the human subject may be infected with RCC (or other solid tumors, depending on the genes used in the diagnosis)" ([0492]), which indicates that further experimentation is needed to at least distinguish RCC from other diseases using gene expression profiles. Thus, it is highly unpredictable to use various individual genes and/or combination thereof, and their expression profiles for diagnosing RCC. Although the instant specification teaches examples of comparing expression profiles RCC samples disease-free samples, the instant specification does not provide all possible combination of genes or individual genes (from the claimed list) that can be used to differentiate RCC from other tumor diseases. In fact, the instant specification discloses the "test set" used for testing the "predicting" power of the various genes for RCC were samples that were known to have RCC (see Example 1, spec). The said examples of the instant specification also do not provide data showing how these "prediction" of RCC and/or other tumors were achieved. For example, over-expression of two genes (such as TLR-2 and EEF1A2) may not create an expression profile to distinguish among different diseases. In addition, data in Table 6 (and [0589] of the spec.) indicates that at least 16 genes are presented only in one sample (a single patient), and more genes are only presented in few than 6 patients (~10% of total sample size), which would not be representative or statistically significant to show possession of the claimed method. This also indicates high unpredictability of using these genes for diagnosing RCC in any human.

The above discussion only illustrated a few problems performing the claimed methods of diagnosing RCC using gene expression profile. Although there may be suggested methods of overcoming these problems through non-routine experimentations, there are no predictable methods or solutions that would solve all the problems for any gene, or combination of genes.

The level of one of ordinary skill

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction or guidance present / The presence or absence of working examples

As discussed above, the instant specification recite examples of using samples derived from patients known to have RCC or persons that were known to be disease-free (see Example 1 of the instant spec.). The instant specification also provides examples (e.g. Example 6) where the expression profiles of genes from RCC patient are compared to diseases free individuals, but not to patients with other diseases. In addition, the instant specification only provides examples of correlating (but not "diagnosing") gene expression profiles from RCC patients with tumors (i.e. later stage of RCC) to disease free individuals. The instant specification does not provide support for the entire claimed genus of methods of "diagnosing" RCC at any stage of the disease. That is applicants have not shown the correlation observed between gene expression profiles of RCC tumor and disease free tissues are predictive to be "diagnostic" of RCC specifically.

The quantity of experimentation needed

Due to the unpredictabilities of the using gene expression profiles of various genes or combinations of genes to diagnosis for a specific disease such as RCC as discussed above, undue experimentation would be required. The art has not demonstrated all the possible genes or combinations of genes as well as their specific expression profiles that can be used to specifically diagnose RCC as discussed above. Because the instant specification only provides guidance of comparing or correlating gene expression profile between diseases-free and RCC patients using known samples, undue experimentation would be required to practice claimed method of diagnosis based on various gene expression profiles.

Conclusion

Therefore based on the evidences as a whole regarding each of the above factors (e.g. factors 1-8), the specification, at the time the application was filed, does not satisfy the enablement requirement for the instant claimed method.

Discussion and Answer to Argument

13. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

As the above rejection is a new rejection under 35 USC 112, 1st paragraph (Enablement Rejection), only the relevant arguments in applicant's reply is addressed below.

Applicants argue the claim amendment is sufficient to overcome the previously set forth written description rejection. (Reply, p.11).

However, applicant's amendments to the claims are not sufficient to overcome the enablement rejection as set forth previously as well as the reasons discussed above.

Applicants cited Example 6 of the instant specification to indicate the instant claimed invention is enabled. (Reply, p.11).

Example 6 of the instant disclosure describes using samples isolated from either patients known to have RCC or "normal PBMC samples" (i.e. disease-free samples) (e.g. [0605]). In the said Example, the "prediction" of RCC is done on the samples of the "test set", which the test set comprise samples from either samples known with RCC or samples that are disease-free (e.g. [[0601]). That is the "comparison" is between a known RCC sample and a normal tissue sample. In this Example, the gene expression profiles of the RCC samples were not compared to other diseased samples (such as other tumor samples), to show a RCC specific differential expression pattern. Further, the said Example 6 also does not show "predicting" or diagnosing RCC using truly "unknown" samples (without prior diagnosis) based on the claimed set (or subset) of genes. That is the instant specification does not have support for a method of "diagnosing" or "predicting" RCC in any individual based on comparison of the expression profiles of any set or subset of genes claimed.

Second paragraph of 35 U.S.C. 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 7 recite the limitation "said one or more RCC disease genes" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/
Patent Examiner, Art Unit 1639
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